General

Guideline Title

Guideline for the diagnosis and management of myelofibrosis.

Bibliographic Source(s)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Molecular Investigations

- *JAK2* V617F mutation screening should be carried out routinely in patients with primary myelofibrosis (PMF). Quantitative results are not required for clinical management.
- *BCR-ABL1* rearrangement should be excluded in cases with atypical trephine biopsy features, or if the patient lacks a mutation in *JAK2* or *MPL*.
- *PDGFRA* and *PDGFB* rearrangements should be excluded in the presence of significant eosinophilia. (Screening for other mutations remains a research tool and routine screening cannot be justified, apart from in cases of diagnostic difficulty where detection of a clonal abnormality would be informative) (Evidence level 2, Grade B).

Prognosis

- Therapeutic decisions in PMF, especially regarding the use of allogeneic stem cell transplantation (allo-SCT), should be based on the patient prognosis as determined by the Dynamic International Prognostic Scoring System (DIPSS) Plus as this is validated for any timepoint of the disease and is more discriminating in median survival prediction than the International Prognostic Scoring System (IPSS) score.
- Whilst the IPSS, DIPSS and DIPSS Plus have not been validated for post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythaemic myelofibrosis (post-ET MF), it is suggested that they still be used in this setting (Evidence level 2, Grade C).

<u>Treatment</u>

Recommendations: Medical Management of Splenomegaly

First Line

- Hydroxycarbamide (in the absence of cytopenias).
- Thalidomide and prednisolone (in presence of cytopenias) - consider lenalidomide (if anaemic with platelet count >100 X 10^9/l).

Second Line

- Consideration should be given to the use of JAK inhibitors either as part of a clinical trial, or via patient access protocols. These agents are now approved in the USA for first-line therapy, which is appropriate following approval (Evidence level 1, Grade A).

Recommendations for Splenectomy

Indications

- Drug-refractory symptomatic splenomegaly
- Drug-refractory anaemia
- Symptomatic portal hypertension (e.g., ascites, bleeding varices)
- Severe catabolic symptoms including cachexia (Evidence level 2, Grade C)

Peri-Operative Management

- Evaluate cardiac, hepatic, renal and metabolic status
- Correction of any coagulopathy
- Meticulous control of platelet count pre- and post-splenectomy
- Laparoscopic splenectomy not advised
- Splenic artery embolization not advised
- Appropriate vaccination and long-term penicillin (Evidence level 2, Grade C)

Post-Splenectomy Myeloproliferation

- Cytoreductive therapy (hydroxycarbamide). Cladribine can be considered in selected patients (Evidence level 2, Grade C).

Recommendations for Radiotherapy

- Patients with symptomatic splenomegaly, who have an adequate platelet count (>50 X 10^9/l) and who are not deemed suitable for surgical intervention. Platelet transfusions may be required post-treatment.
- Extramedullary haematopoiesis (EMH) involving vital organs
- Severe bone pain (Evidence level 2, Grade C)

<u>Treatment of Anemia</u>

Transfusion Recommendations

- Red cell transfusions are recommended in PMF patients with symptomatic anaemia (Evidence level 2, Grade B).
- Iron chelation therapy is not routinely recommended in PMF (Evidence level 2, Grade B).

Recommendations for Erythropoietin

- A trial of recombinant human erythropoietin (rEPO) therapy should be considered in anaemic PMF patients with inappropriately low erythropoietin levels (<125 u/l). Responses are more likely in those with relatively moderate anaemia (Evidence level 2, grade B).
- rEPO should be commenced at a dose of 10,000 units three times weekly (or darbepoetin 150 µg weekly) doubling to 20,000 three times weekly (darbepoetin 300 µg weekly) after 1–2 months in the absence of an early response. Treatment should be discontinued after 3–4 months if no response occurs (Evidence level 2, grade B).

Recommendations for Androgens

- Danazol should be considered as a therapeutic option to improve the haemoglobin concentration of patients with myelofibrosis and

transfusion-dependent anaemia (Evidence level 2, Grade B).

- Recommended starting dose is 200 mg daily, with a gradual dose escalation, depending on tolerability and patient weight (to a maximum of 600 mg daily for patients <80 kg and 800 mg for patients >80 kg) (Evidence level 2, Grade B).
- Patients should be treated for a minimum period of 6 months. Responding patients should be maintained for a further 6 months on 400 mg daily before titrating down the dose to the minimum required in order to maintain a response (Evidence level 2, Grade B).
- Liver function tests (LFTs) should be monitored at least monthly initially and liver ultrasound is recommended every 6–12 months to exclude hepatic malignancy (Evidence level 2, Grade C).
- Male patients should be screened for prostate cancer before and during therapy (Evidence level 2, Grade B).

Management of Constitutional Symptoms

Recommendations for Constitutional Symptoms

- Management of constitutional symptoms in PMF is challenging and there is no evidence of benefit for conventional agents in this area. Patients with profound symptoms are usually in the poor risk group and should be considered for experimental therapy with JAK inhibition (Evidence level 1, Grade A).

Myelosuppressive Therapy

Recommendations for Myelosuppressive Therapy

- Hydroxycarbamide is the first-line choice for the control of the hyperproliferation manifestations of myelofibrosis (Evidence level 2, Grade B).
- Anagrelide should be used with caution in patients with established myelofibrosis (Evidence level 2, Grade B).
- The use of α-interferon (IFN-α) in PMF patients should be restricted to cases with early phase disease with more proliferative disease features (Evidence level 2, Grade B).
- High starting doses of conventional IFN-α are very poorly tolerated in PMF and should be avoided. When conventional IFN-α is used, it is recommended to commence at 1.5 million units three times per week and increase to a maximum of 1.5 million units/week as tolerated. If using pegylated-IFN, α2a is the recommended agent (Evidence level 2, Grade B).

Bone Marrow Transplantation

Recommendations for Allogeneic Haemopoietic Stem Cell Transplantation (Allo-HSCT)

Definition: A transplant-eligible patient is defined as one deemed fit enough to undergo the procedure with manageable co-morbidities and having a human leucocyte antigen (HLA) matched sibling or unrelated donor available.

- Transplant-eligible patients <45 years of age, with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, should be considered for myeloablative (MA) allo-HSCT (Evidence level 2, Grade C).
- Transplant-eligible patients with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, together with an HSCT co-morbidity index ≥3, or who are aged over 45 years, should be considered for reduced intensity conditioning (RIC) allo-HSCT (Evidence level 2, Grade C).
- Patients should be transplanted before they have received more than 20 units of red cells (Evidence level 2, Grade C).
- Use of oral busulfan should be accompanied by targeted dosing according to plasma levels. Alternatively, intravenous busulfan can be used, guided by plasma levels where possible (Evidence level 2, Grade C).
- There is no convincing evidence for pre-transplant splenectomy and some evidence of harm both from surgical morbidity and mortality and a possible increased risk of relapse post-transplant (Evidence level 2, Grade C).
- *JAK2* V617F mutated patients monitored by quantitative polymerase chain reaction (Q-PCR) posttransplant who do not achieve or who relapse from molecular complete response (CR) are candidates for donor lymphocyte infusions in the absence of graft-versus-host disease (GvHD) (Evidence level 2, Grade B). The role of Q-PCR for other mutations post-bone marrow transplantation remains unclear.
- There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favourable results have been achieved following busulfan combined with cyclophosphamide (BUCY) and fludarabine combined with busulfan (FLUBU) and anti-lymphocyte globulin. Every effort should be made to enroll patients in prospective clinical studies and data reported to National and International Registries (Evidence level 2, Grade C).

Recommendations for Management of Primary Myelofibrosis-Blast Phase (PMF-BP)

- PMF-BP has a poor prognosis and consideration should be given to strictly supportive care (Evidence level 2, Grade B).

- Azacitidine (75 mg/m^2 for 7 days every 28 days) as a single agent can lead to responses of a palliative, or possibly life-prolonging, nature for patients who will not be candidates for allo-SCT (Evidence level 2, Grade C).
- A curative approach for PMF-BP requires the success of induction chemotherapy, with a return to a chronic phase disease, and an immediate allogeneic stem cell transplant. Rigorous candidate selection is needed, given that these challenging steps are likely to be successful in only a minority of patients (Evidence level 2, Grade B).

Management of Pregnancy

Recommendations

- Pregnancy is a rare event in PMF and data should be prospectively collected. Management according to current guidelines for thrombocythaemic (ET) myelofibrosis is suggested (Evidence level 1, Grade C).

PMF in Childhood

Recommendations for PMF in Children

- A conservative approach is recommended for most cases. A trial of steroids should be considered, once acute megakaryoblastic leukaemia (AMKL) and vitamin D deficiency have been excluded (Evidence level 2, Grade B).

JAK Inhibitors

Recommendations

- A number of JAK inhibitors are at various stages of clinical development and a consistent pattern of response in splenomegaly and disease-related symptoms is emerging. Initial data from a Phase III study suggests survival may be improved. Further data with regards to effects upon survival and leukaemic transformation are awaited. Current recommendation to consider referring patients, who have failed hydroxycarbamide therapy and are not presently suitable for bone marrow transplantation (BMT), for trials with JAK inhibitors (Evidence level 1, Grade A). Should these agents be approved then they would be considered as first-line agents for patients with troublesome splenomegaly and disease-related symptoms (Evidence level 1, Grade A).
- See additional recommendations with regard to splenomegaly and management of symptoms.

Definitions:

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of Evidence

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Myelofibrosis

Other Disease/Condition(s) Addressed

- Anemia
- Splenomegaly

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Hematology

Oncology

Intended Users

Physicians

Guideline Objective(s)

To provide a practical, rather than a research, approach to the diagnosis, investigation and management of patients with primary, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythaemic myelofibrosis (post-ET MF) in both adult and paediatric patients

Target Population

Adult and paediatric patients with primary myelofibrosis, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythaemic myelofibrosis (post-ET MF)

Interventions and Practices Considered

Diagnosis/Evaluation

1. Molecular investigations (screening for *JAK2 V617F* mutation, BCR-ABL1 rearrangement, and other mutations)
2. Therapeutic decision-making based on formal prognostic scoring systems (Dynamic International Prognostic Scoring System [DIPSS], DIPPS Plus)

Treatment/Management

1. Medical management of splenomegaly
   - First line: hydroxycarbamide, thalidomide and prednisolone, lenalidomide
   - Second line: JAK inhibitors
2. Splenectomy, including perioperative management and management of post-splenectomy myeloproliferation
3. Radiotherapy
4. Treatment of anaemia
   - Transfusion
   - Recombinant human erythropoietin (rEPO)
   - Androgens (e.g., danazol)
5. Management of constitutional symptoms
6. Myelosuppressive therapy
   - Hydroxycarbamide
   - Anagrelide
   - Interferon-α
7. Allogeneic haemopoietic stem cell transplantation (allo-HSCT)
8. Management of blast phase of myelofibrosis (supportive care, azacytidine, stem cell transplant)
9. Management of primary myelofibrosis (PMF) in pregnancy
10. Management of PMF in children
11. Use of novel therapies (JAK inhibitors)

Major Outcomes Considered

- Clinical or informative benefit of mutation screening
- Prognostic accuracy of international scoring systems
- Candidate risks and benefits of surgical treatment
- Treatment efficacy and clinical response rates
- Overall and disease-free survival
- Transplant-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

MEDLINE and EMBASE were searched systematically for publications in English from 1966 until August 2011 using a variety of key words.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The criteria used to state levels and grades of evidence are as outlined in the Procedure for Guidelines commissioned by the British Committee for Standards in Haematology (BCSH); the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to score strength and quality of evidence (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group regarding the diagnosis and management of myelofibrosis was selected to be representative of UK-based medical experts, together with a contribution from a single expert from the USA.

The writing group produced the draft guideline, which was subsequently revised by consensus of the members of the General Haematology and Haemato-oncology Task Forces of the British Committee for Standards in Haematology (BCSH).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of UK haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Improved diagnosis, investigation and management of patients with primary, as well as post-polycythaemic myelofibrosis (post-PV MF) and post-thrombocythaemic myelofibrosis (post-ET MF)
- Improved prognosis

Potential Harms

- Busulfan may produce clinical benefit, but myelosuppression and an increased risk of acute leukaemia are potential adverse factors.
- Hydroxycarbamide benefit is usually seen within 8–10 weeks of treatment, although side effects, especially significant cytopenias, may be problematic at effective doses.
- Myelosuppression is a significant side-effect of cladribine.
- Regular transfusions will eventually lead to iron overload, although it remains unclear whether this leads to toxicity and end-organ damage.
- Interferon-α has a particularly high rate of toxicity in primary myelofibrosis (PMF).
- Data from the Primary Thrombocythaemia 1 study and the Swedish Myeloproliferative Disorder Study Group have suggested that anagrelide treatment, when compared with hydroxycarbamide, may be associated with an increase in reticulin grade. As a consequence, the BCSH guidelines for the investigation and management of patients presenting with thrombocytosis suggest regular monitoring for development of MF in patients treated with this agent and a change of therapy should this occur.
- Androgen side effects are well recognized including fluid retention, increased libido, hirsutism, deranged liver function tests (LFTs) and hepatic tumours. Male patients should be screened for prostate cancer before and during androgen therapy.
- Even in the best units, splenectomy is associated with morbidity and mortality rates of approximately 31% and 9%, respectively. Hepatic extramedullary haematopoiesis leading to rapid hepatic enlargement is an unusual but well recognized complication and unexpectedly high rates of leukaemic transformation have been documented; the latter finding is believed to relate to patient selection, rather than a true alteration in the disease biology, as there is no reason to believe disease biology, related to clonal stem cell abnormality, would be altered by splenectomy. Importantly, a significant post-operative thrombocytosis is observed in approximately 20% of patients and carries an increased thrombotic risk. It is for this reason that normalization of platelet counts pre- and post-splenectomy is strongly recommended. Furthermore, cladribine may be considered as a palliative option for patients with post-splenectomy myeloproliferation that is refractory to hydroxycarbamide.

Qualifying Statements

Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society of Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe A, Green AR, George Michaeel N, Gilleece MH, Hall GW, Knapper S, Mead A, Mesa RA, Sekhar M, Wilkins B, Harrison CN, Writing group: British Committee for Standards in Haematology. Guideline for the diagnosis and management of myelofibrosis. Br J Haematol. 2012 Aug;158(4):453-71. [123 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Aug

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

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Financial Disclosures/Conflicts of Interest

None of the authors have any competing financial interest or conflict of interest associated with these guidelines.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 6, 2012.

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